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July 22, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 2004-N-0181

Dear Sir or Madam:

We are pleased to submit the following comments and recommendations regarding the FDA's "Critical Path Initiative." 69 Fed. Reg. 21839 (Apr. 22, 2004). We would like to applaud the FDA for soliciting public comment on ways the agency, regulated industry and other stakeholders can work together to help decrease research and development (R&D) costs and increase the speed and efficiency of approvals for safe and effective medical products.

Although there are many "hurdles" to overcome in the current product development paradigm, the following comments relate specifically to the time and expense currently spent during the clinical trial process when sponsors employ tools and techniques that fall short of industry best practices. In some instances, sponsors are unaware of superior competing paths for testing and developing products, which leads to duplicative, inefficient or substandard work and product approval delays. The FDA is in a unique position to help mitigate these and related problems provided it can balance, among others, the competing priorities of swifter product approvals and vigilant preservation of trade secret data. To this end, we respectfully suggest that the agency consider establishing and funding a voluntary "Critical Path R&D Repository."

I. FDA Critical Path R&D Repository

An FDA Critical Path R&D Repository as proposed (see Attachment A) would provide a ready means to aggregate and organize clinical and pre-clinical research data generated by sponsors and researchers, the FDA, the National Institutes of Health, and others across the entire spectrum of drug, biologics and medical device research. This project also would respond to and complement initiatives relating to clinical trial registry and enforcement that have received significant attention in recent months. For instance, the Pharmaceutical Research and Manufacturers of America, has issued a voluntary set of principles "urging drug companies to publish trial results, regardless of whether they are positive or negative, in journals, present them at scientific meetings, or post them on the internet."[1] Similarly, The American Medical

[1] Scott Hensley, *Drug Makers Urged to Publish Data—Industry Guidelines Aim to Quell Any Suspicions About Negative Findings*, The Wall Street Journal, June 30, 2004, at D7. See also *PHRMA Clinical Trial Guidelines Stress Timely Release of Data, With Caveats*, 66 (27) The Pink Sheet 3 (July 5, 2004).

Association (AMA), recently approved a policy urging the federal government to develop and require a public registry for all clinical trials and their outcomes.[2]

Data in the proposed Critical Path R&D Repository, in addition to a registry of clinical trial programs underway or in planning stages, also would include information that could be used by sponsors to develop more informed and rational clinical trials and research designs. This could contribute to making clinical trial design less "hit and miss" and more evidence-based and grounded in historical data, analyses and lessons learned. Some of this data would require redaction of trade secret and proprietary information, but the FDA could encourage sponsors to make available via the Repository "non-core" information previously considered proprietary.

Areas of focus for content data could include, among others, potential side effect profiles for various classes of drugs; better understanding of toxicity by drug classes; better identification of potential trial endpoints; better understanding of potential confounders in Phase IV studies; and better information bases for clinical trials computer modeling and simulations.

Including the above types of information in an organized, publicly accessible electronic Repository could lead to speedier clinical testing times and FDA application reviews. Sponsors could develop and pre-check prospective drug discovery projects and FDA submissions against a "common ground" database of Critical Path do's and don'ts. Sponsors also could use the data to make more rapid decisions on whether to continue or abandon investigational products based on whether data sufficient to prove safety and efficacy to the FDA are likely to come from further investment. This would be possible through comparisons of study design and outcome expectations to other studies and similar past experiments and trials done by other companies. Sponsors would benefit from information gleaned from other industry participants' past submissions to the FDA. Consequently, the FDA would receive more thorough and consistently higher quality drug or device approval applications, which generally would lead to shorter review times by the agency.

Information in the Repository could assist the FDA in establishing better and more precise standards for review of investigational new drug applications (INDs), new drug applications (NDAs) and post-market surveillance activities. Also, the Repository database could be used to facilitate technology transfer in a "safe harbor" environment. This could be very attractive to sponsors and researchers as it could be used to free up non-core assets that currently are on the shelf but which could be used and/or developed by other entities.

II. A Proven Model

Although our concept for an FDA Critical Path R&D Repository is unique, it builds on successful models used elsewhere. For example, the SNP Consortium, Ltd.[3], was created in 1999 as a non-profit foundation for the purpose of providing single nucleotide polymorphisms (SNPs) human genomic data to the public without

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[2] See *AMA Supports Public Registry For Clinical Trials, Outcomes*, The Wall Street Journal, June 16, 2004, at D2.

[3] See http://snp.cshl.org; and Thorisson GA & Stein LD, *The SNP Consortium Website: Past, Present and Future*, 31 (1) Nucleic Acids Research 124-27 (2003).

intellectual property restrictions. The foundation is supported by many international companies and research institutions, including: Amersham Biosciences, AstraZeneca, Aventis, Bayer, Bristol-Myers Squibb, Cold Spring Harbor Laboratory, F. Hoffman-La Roche, GlaxoSmithKline, IBM, Motorola, Novartis, Pfizer, Searle, Stanford University, Washington University, the Wellcome Trust and the Whitehead Institute.

A number of other public-private health sciences research partnerships are based on Cooperative Research and Development Agreement (CRADA) relationships. Created as a result of the Stevenson-Wydler Technology Innovation Act of 1980[4], as amended by the Federal Technology Transfer Act[5] of 1986, a CRADA allows the federal government and non-federal partners to optimize their resources, share technical expertise in a protected environment, share intellectual property emerging from the effort and speed the commercialization of federally developed technology. Public-private partnerships regularly are used to facilitate basic research and technology transfer in the defense, information technology and other high technology sectors. This type of relationship is expressly embraced and supported by the Federal Technology Transfer Act of 1986 and Executive Order No. 12591[6], among others.

The FDA could organize and manage the proposed Repository, or advertise, facilitate and support its launch via an independent or affiliated non-profit organization like the SNP Consortium.

III. Sponsor Incentives

We contemplate that participation in the Repository would be voluntary for sponsors given the current landscape surrounding disclosure of clinical trial data. However, there would be an important incentive for sponsors to participate in the project. For instance, Reuters recently reported that GlaxoSmithKline "would create an electronic database to be called GSK Clinical Trial Register, which it plans to make accessible very soon to doctors and the public."[7] Further, *The Washington Post* reported recently that the World Health Organization (WHO) will propose an international registry of drug trials in November.[8] The article noted that this registry would be based on registries in the U.S. and other countries. The International Committee of Medical Journal Editors (ICMJE), which includes 12 of the leading international medical journals, also is considering a proposal to require drug sponsors to register clinical trials in a public database for results to later be considered for publication.[9] These initiatives—and the PhRMA set of principles and AMA policy mentioned

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[4] Stevenson-Wydler Technology Innovation Act, Pub. L. No. 96-480 (1980).
[5] Federal Technology Transfer Act, Pub. L. No. 99-502 (1986).
[6] Executive Order 12591, Facilitating Access to Science and Technology (1987). The Order assures that government-owned or government-operated (GOGO) laboratories can enter into "cooperative research and development agreements with other Federal Laboratories, state and local governments, universities, and the private sector." Under this system, federal laboratories must apprise these parties about their technology transfer opportunities. The Order established the "Technology Share Program" and "Basic Science and Technology Centers" with university partners.
[7] Mark Potter and Ransdell Pierson, *Glaxo to Publish Drug Trial Results Online*, Reuters (visited 7/8/04) http://www.biz.yahoo.com/rb/040618/health_gsk_3.html.
[8] Shankar Vedantam, *WHO Wants to Start Drug Trial Registry*, The Washington Post, July 8, 2004, at A3.
[9] See Barry Meier, *Group Weighs Plan for Full Drug-Trial Disclosure*, The New York Times, June 15, 2004, at 1.

earlier—should help assuage growing public doubts about the completeness and accuracy of clinical trial data reporting.[10] Similarly, through the proposed repository, the FDA and data contributors could produce and maintain a powerful and centralized Repository that could positively affect the overall drug development and approval process in addition to increasing public goodwill toward the industry and solving smaller information gap issues.

Further, by providing access to a platform containing previously closely-held information regarding pre-clinical and clinical research project designs, companies would benefit from the knowledge from past successes and failures for similar projects and/or products. Sponsors stand to benefit by increasing the return on investment for their enormous research budgets by: 1) increasing the likelihood of gaining FDA approval by modeling trials and research projects after previously successful applications conducted by and/or submitted for approval by competitors, (this would be particularly useful for projects in new therapeutic areas in which companies do not have their own established R&D submission protocols as with other therapeutic areas); 2) increasing the speed of FDA approval due to less "back and forth" between the sponsor and agency during the approval process; and 3) enabling earlier abandonment or modification of projects or trials that are likely to fail to achieve regulatory approval based on historical data on similar trial designs or product applications.

It is reported that the FDA eventually approves 75 percent of applications for new molecular entities (NMEs), but that fewer than 40 percent of NMEs are approved on the first FDA review cycle.[11] And by one industry analyst's estimate, for every month delay in FDA regulatory approval, it can cost a sponsor nearly $42 million in lost revenue.[12] Taken together, these numbers demonstrate that there should be a clear incentive for sponsors to participate in a voluntary Repository to help reduce costs associated with lost market opportunities from FDA approval delays.

In addition to the above benefits, sponsors would be further incentivized to contribute to the Repository because they could receive additional benefits in the form of federal tax breaks. Charitable donation tax benefits generally are available for donations of intellectual property to federal agencies for public purposes. Sponsors can donate unused or non-core intellectual property resulting from research or experimental expenditures. Because the Repository has a public mission, sponsor donation of an IP asset with third-party, fair-market valuation could result in federal tax benefit to the sponsor/donor.

IV. FDA Incentives

The incentives to the FDA for initiating and supporting such a project are many. First, the FDA currently has no mechanism for disseminating non-core proprietary or

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[10] See, e.g., Barbara Martinez, *Spitzer Charges Glaxo Concealed Paxil Data*, The Wall Street Journal, June 3, 2004, at B1.

[11] See *CDER: Better Molecular Entity Applications Needed*, 36 (25) Washington Drug Letter, June 21, 2004.

[12] See Adam Feuerstein, *FDA Not Solely to Blame for Drug-Approval Delays*, TheStreet.com (Sept. 26, 2001) (quoting Merrill Lynch analyst Steven Tighe); and Lewis Krauskopf, *Nation's Drug Makers in Need of a Quick Fix; Industry Hurt By Slowdown in FDA Approval*, The Record, Dec. 30, 2001, at 4.

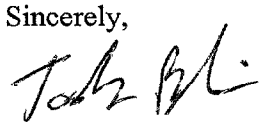
trade secret submission data from one sponsor to other sponsors. This information would be useful to other sponsors when constructing their own submissions to FDA. By having sponsors model their submissions on previously successful formats, content, study designs and data analyses techniques, the FDA would have the benefit of reviewing more standardized submissions, which would reduce the back-and-forth delays during the approval process, and thus reduce overall approval times. The availability of such a mechanism could evolve into a "guidance-like" platform on which sponsors could model their submissions, and as such, would streamline and standardize the way in which applications are reviewed and approved. Sponsors could access, employ and model study design and analysis based on best practices for achieving FDA approval, including: 1) easier to review IND information and data; 2) more efficient and precise clinical trial design (e.g., including more sensitive rule-in criteria and subpopulation information); 3) better data and information to assess safety risk before or while trial is in progress; 4) better reference standards; 5) better information concerning potential biomarkers and surrogate endpoints; 6) heightened ability to conduct pharmacovigilance studies; and 7) other related benefits.

The initiation and support for such a program—especially in light of the recent media attention surrounding transparency of medical research—would serve the agency well by demonstrating to the public and other stakeholders a novel way for the FDA to speed up drug approvals and decrease R&D costs. Further, this effort would enable the FDA to respond to international calls by ICMJE, the WHO, the AMA and others for public clinical trial data registries and other transparency initiatives with a credible and robust program that will support the industry sponsors and protect the public interest.

We propose that the FDA initiate and support a Critical Path R&D Repository to directly address these and similar issues, and to further complement its commitment to shortening drug and device approval times and to minimizing unnecessary health care costs. We would be pleased to discuss these recommendations in future public forums or other venues regarding the FDA's Critical Path Initiative.

We are pleased to submit the above for consideration, and note that the views expressed are those of the undersigned and do not necessarily reflect the views of Ernst & Young LLP.

Sincerely,



Leslie A. Platt, William Alexander, Philip Cyr, Joshua Berlin & Andrew Schofield

Attachment A

Schematic of Proposed FDA Critical Path R&D Repository

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